Excitable Cells: Passive Properties

Introduction

Cell membranes are **lipid bilayers** and are **impermeable to ions**. Ions, even as small as they are, require **channels** to let them through because they cause a charge. Thus, ions flow only when the normally impermeable membrane becomes permeable because of channels. Channels can be opened by voltage changes (**voltage-gated**), opened by the binding of a receptor (**ligand-gated**), physically opened by the ligand (**mechanically gated**), or always open (**leak**).

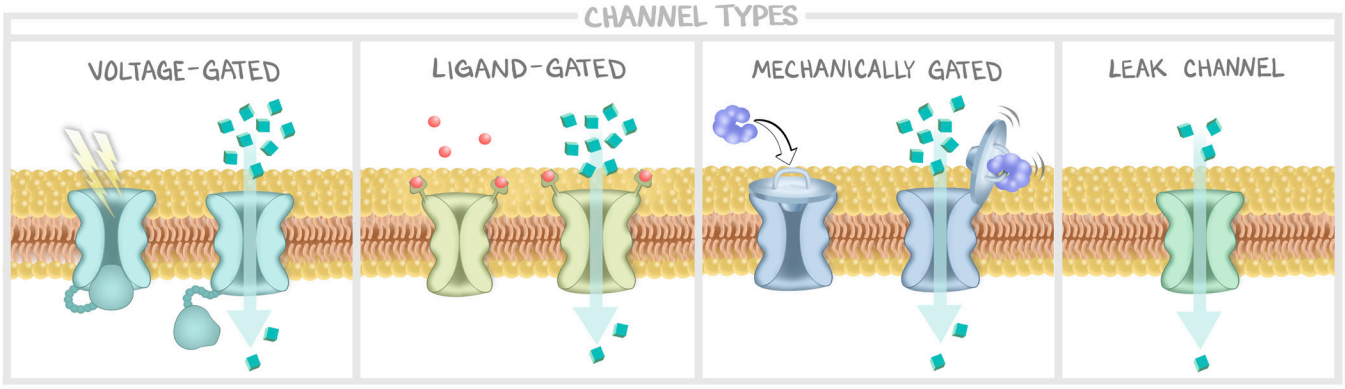

Figure 6.1: Types of Channels
Different channels exist within cell membranes to allow small molecules (usually ions) to pass through the membrane. Some are activated by voltage, some by ligands, some mechanically, and others remain always open.

The forces that drive the ion in a certain direction are both **chemical** (the concentration gradient) and **electrical** (based on ionic charge). The electrical force that balances the chemical force is called the **equilibrium potential**, calculated by the Nernst equation, and so also referred to as the **Nernst potential.** When a cell membrane becomes permeable to an ion, the ion will move down its concentration gradient. To compensate for that change in chemical force, the membrane potential (voltage across the membrane) will change, bringing the cell closer to that ion's **Nernst potential**.

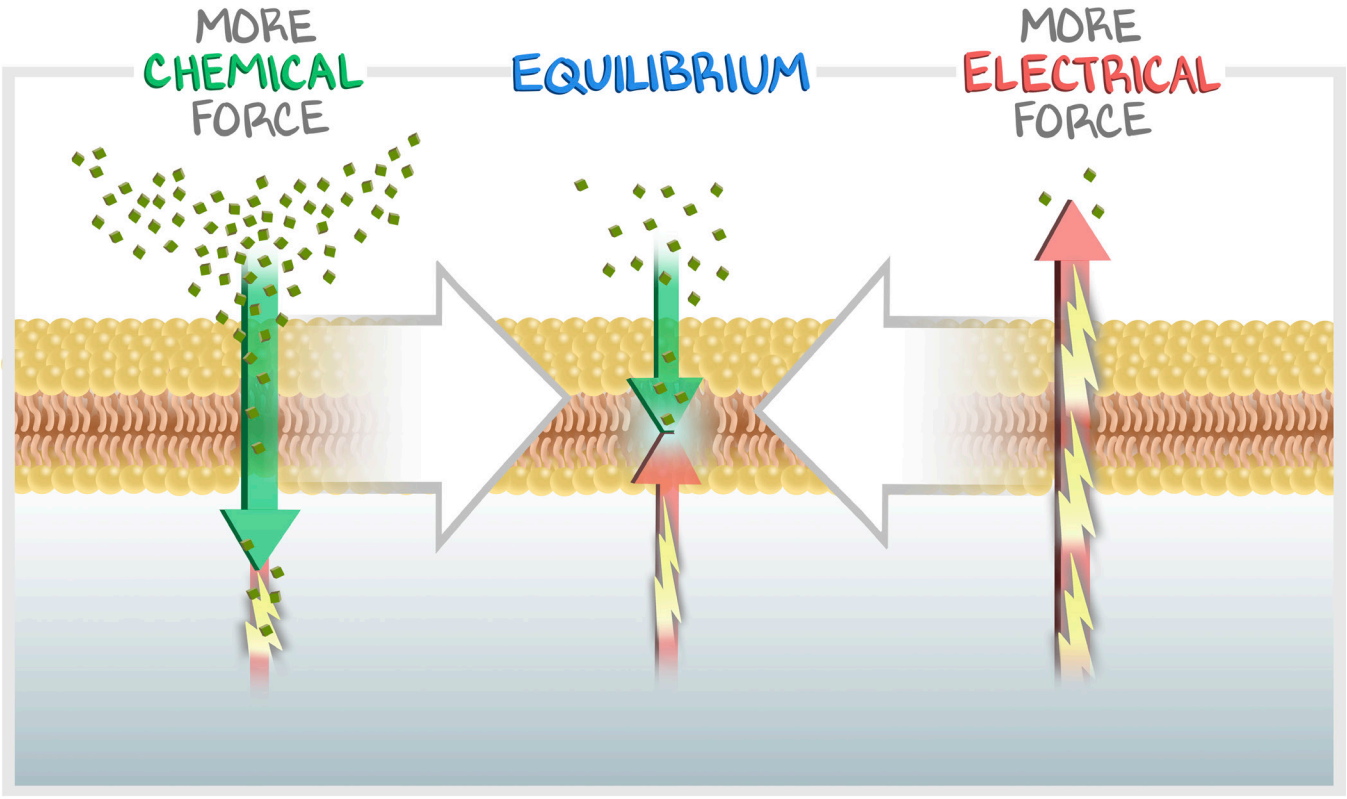

Figure 6.2: Chemical and Electrical Forces
The concentration gradient establishes a chemical force. We scientists can inflict a voltage such that the electrical force will balance the flow of ions or even reverse the flow of ions. When a cell membrane becomes permeable to an ion, the ion will move down its concentration gradient. To balance the chemical force, the membrane voltage will shift towards that ion's equilibrium potential.

For example, let's look at the two most important ions: potassium and sodium. The Nernst potential for potassium (K^+) is −95. If the cell became permeable to K^+, and K^+ only, and infinitely permeable to K^+, the cell potential would go to −95. The Nernst potential for sodium (Na^+) is +65. If the cell became permeable to Na^+, and Na^+ only, and infinitely permeable to Na^+, the cell's membrane potential would go to +65.

Membrane conductance is how permeable the membrane is to an ion. Permeability and conductance are going to be used interchangeably in this lesson. Membrane conductance is a product of the number of open channels (total number of channels × % of open channels) and how well those channels conduct that ion.

Membrane Conductance = Number of Channels × % Open × Channel Conductance

An increase in any of the factors will increase the membrane conductance. The higher the membrane conductance, the faster those ions will move and the faster the cell membrane will approach that ion's Nernst potential. Thus a membrane with a **higher conductance approaches the Nernst potential faster.**

Establishing a Resting Membrane Potential

An excitable cell has a **constant resting membrane potential**, meaning the voltage is always about the same until ions start to move. There are different resting membrane potentials in different cells within the body. For example, it's –90 in ventricular myocytes. However, in most cells, the resting membrane potential is –70, so that is what we will use in our examples here. Let's discuss how that is created.

First, all cells have the **Na^+/K^+-ATPase** pump, which uses the energy from hydrolysis of ATP to move sodium (Na^+) and potassium (K^+) against their concentration gradient. **Three Na^+** are pumped out while **2 K^+** are pumped in. With more "positive" moved out than in, the cell becomes **more negative** inside just from this pump alone, even without engaging Nernst potentials.

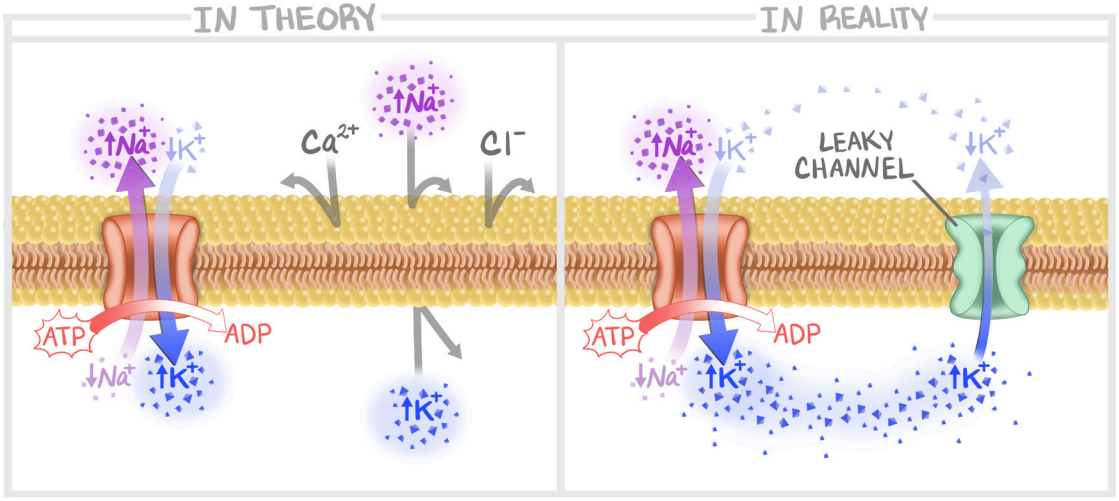

Figure 6.3: Establishing the Resting Membrane Potential
Theoretically, the plasma membrane itself is impermeable to ions. At rest, an excitable cell uses ATP to pump 3 Na^+ out of the cell and bring 2 K^+ in, against their concentration gradients. In reality, due to the presence of potassium leak channels within the membrane, potassium can also slowly move down its concentration gradient at rest and towards its Nernst potential.

With that concentration gradient established, Na^+ wants to get into the cell and K^+ want out. **At rest**, the cell membrane is **mostly impermeable**, but the presence of **potassium leak channels** allows potassium to move across freely. However, these channels are few in number and have poor channel conductance, so **membrane conductance to potassium is low**—potassium doesn't rush out. Since membrane conductance to all other ions is nonexistent, the cell slowly approaches the Nernst potential for potassium (–95), with potassium flowing down its concentration gradient through the leak channels to exit the cell.

If there were only leak channels, meaning the cell were permeable only to potassium and only at rest, the membrane potential would be the Nernst potential for K^+. There are other ion channels, but they have such low membrane conductance at rest that they don't substantially affect the resting membrane potential. However, the Na^+/K^+-ATPase continues to bring K^+ into the cell despite the leak channels letting it out, so the resting potential actually stays around –70 mV in real cells.

You should now be able to understand why ventricular myocytes, with a resting potential of –90, are closer to the Nernst potential for potassium. The myocyte membrane has higher conductance for potassium at rest, thus allowing more to move down the gradient to exit the resting cell, keeping it more negative.

Polarization

A cell membrane can move away from its resting potential in two ways, becoming either more positive or more negative. When a cell becomes more positive, it is called depolarization. To **depolarize** means "to undo the polarity," to reverse the negative charge. Depolarization moves the cell toward the Nernst potential of sodium (+65 mV) and, to a lesser degree, calcium.

When a cell becomes more negative, it is called hyperpolarization. To **hyperpolarize** means "to gain more polarity," to make the negative charge larger. This moves the cell toward the Nernst potential of potassium (–95 mV) and, to a lesser degree, chloride.

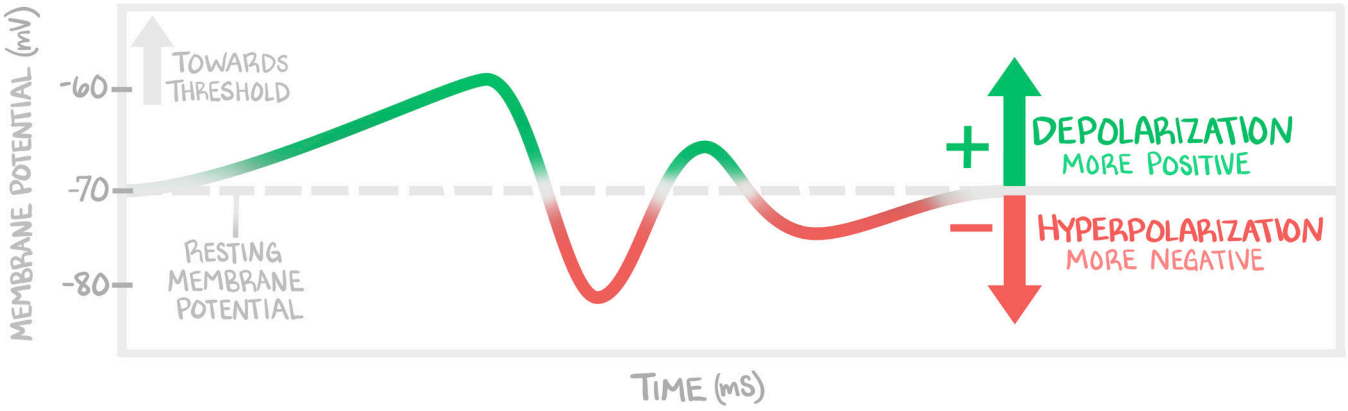

Figure 6.4: Hyperpolarization vs. Depolarization
If a channel opens and the cell becomes permeable to an ion, the ion will move down its concentration gradient. In doing so, it will move the local membrane potential closer to that ion's equilibrium potential, that ion's Nernst. What you should take away is that any stimulus that heads towards zero, that is, in a positive direction, is a depolarizing stimulus, and is probably Na^+ or Ca^{2+}. Any stimulus that heads more negative from resting is a hyperpolarizing stimulus, and is probably K^+ or Cl^-. This is an obvious oversimplification, but it works.

Potassium and the Resting Membrane Potential

Because the resting membrane potential is dependent on potassium leak channels, and because potassium leak channels allow for movement of potassium based on the concentration gradients, alterations in the extracellular potassium can have an effect on that resting potential.

Hypokalemia (low circulating potassium) means there is less potassium outside the cell. This increases the concentration gradient, and so more potassium flows out of the cell, making the cell more negative. You can also think about it this way: as the gradient increases, the membrane conductance of potassium increases, driving the cell closer to the Nernst potential for potassium. "*Drive toward the Nernst potential for potassium*" and "*make more negative*" both mean the same thing—**hypokalemia hyperpolarizes the cell**.

In contrast, **hyperkalemia** decreases the concentration gradient, causing more potassium to remain in the cell, making the cell more positive. Membrane conductance, and thus flow of potassium out of the cell, decreases, moving the cell away from the Nernst for potassium, and **depolarizing the cell**.

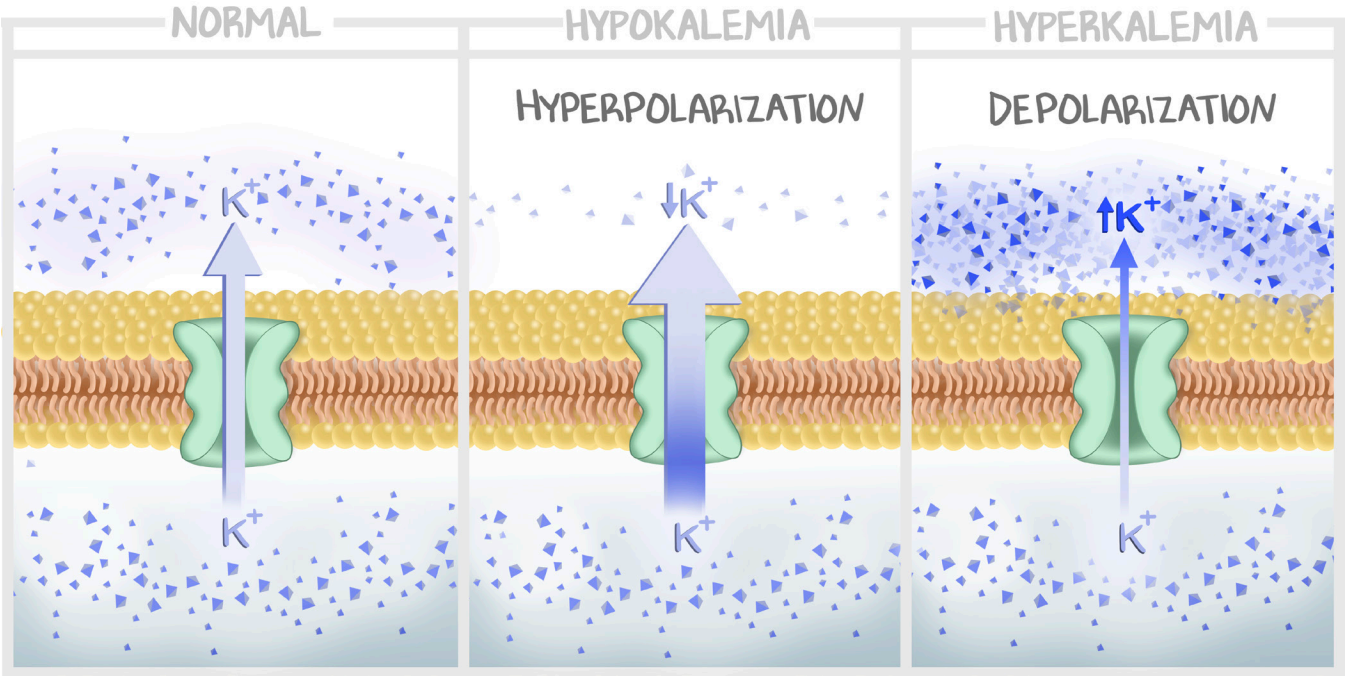

Figure 6.5: Effects of Serum Potassium on Excitability
Hypokalemia (low serum potassium) increases the concentration gradient compared to a normal cell at rest, so more potassium exits through leak channels. The cell moves toward the Nernst of potassium as it becomes hyperpolarized. Hyperkalemia (high serum potassium) lowers the gradient, causing less potassium to leave the cell. The cell becomes depolarized (more negative) as it moves away from the Nernst of potassium.

Because the resting membrane is **not permeable** to Na^+, Ca^{2+}, or Cl^-, these ions do not significantly alter the resting membrane potential. Only **extracellular potassium** changes have meaningful impact on excitable cells, such as cardiac myocytes. This is also why small variations in the potassium can be fatal—the normal serum potassium is 3.5–5.0, with lethal concentrations at 7.0.

Subthreshold Stimulus

When a stimulus is applied to an excitable cell, the membrane becomes more permeable to Na^+, which moves into the cell, causing it to **depolarize**. If it remains **below the threshold** potential, an action potential is not generated. With increased Na^+ permeability, the cell moves toward sodium's Nernst potential (+65). These new positive charges (Na^+) encounter the positive charges already in the cell (K^+), and they don't really get along. As Na^+ is careening down its concentration gradient—into the cell—it creates an electrical force which drives the potassium to escape through the leak channels. The Na^+/K^+-ATPase then pumps the sodium back out of the cell and the potassium back in, to ultimately re-establish the resting potential.

Subthreshold stimuli are different from threshold stimuli in a few ways. They are **graded** (i.e., NOT all-or-nothing), with the degree of depolarization proportional to the magnitude of the stimulus. These stimuli will degrade over distance and time. However, they can also be summative if occurring temporally close together, which could result in the final stimulus after a series of subthreshold stimuli actually reaches the threshold potential. If the threshold is not reached, they will always return to the resting potential.

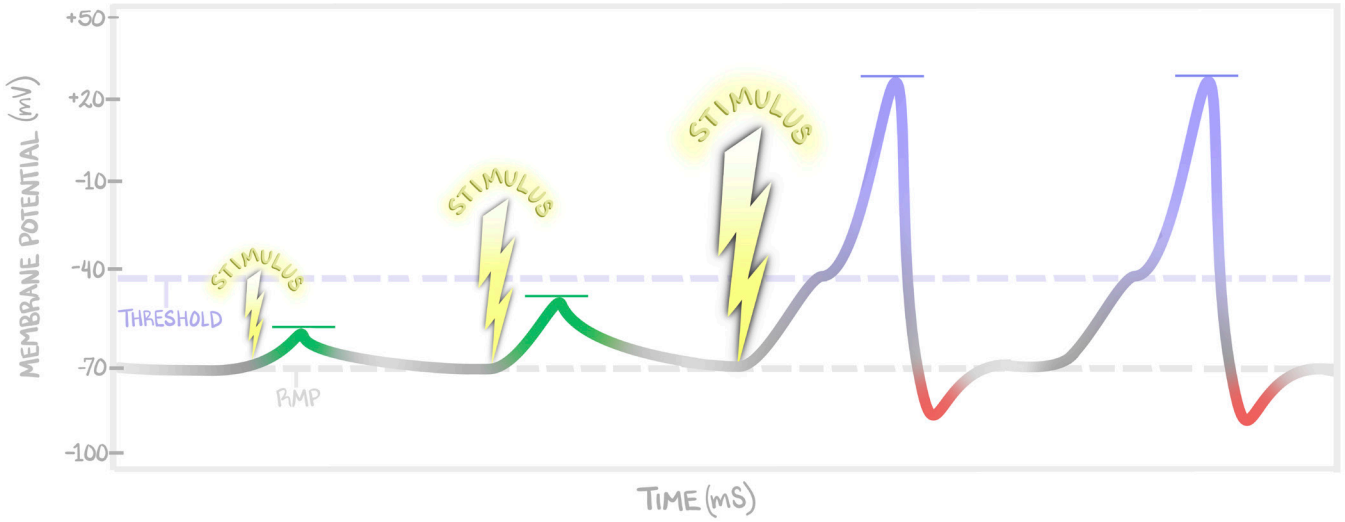

Figure 6.6: Electrical Signals
Subthreshold stimuli create graded electrical signals which lessen over time and distance and do not reach threshold potential. Action potentials occur when the threshold potential is reached, resulting in an all-or-nothing response that regenerates after completion.

Threshold Stimulus

If enough depolarization occurs to an excitable cell, it will cross the **threshold potential**, and an action potential will occur. The threshold potential is a local phenomenon whereby the voltage change caused by **non-voltage-gated channels** is sufficient to cause specialized **voltage-gated Na^+ channels to open**. If the threshold is reached, ALL local channels open. If it's not reached, NONE of them opens. Hence, "all-or-none."

Each voltage-gated sodium channel possesses both an activation and an inactivation gate. At rest, the activation gate is closed, and the inactivation gate is open. When the threshold is crossed, the **activation gate** undergoes a conformational change and opens. Once the threshold is met, all of these channels open on that cell's membrane. This massively shifts the membrane conductance of ions and drastically changes the cell membrane's potential. What happens next—the action potential—is the topic of the next lesson.